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Synthesis, Characterization and Application of Mannich Base

Rashmi Bhardwaj[1], Poonam Parihar[2], Komal Yadav[3], NB Bardhan[4]

[2]Assistant Professor, [1,2]Department of Chemistry, IIS University, Jaipur, Rajasthan, India
[3]Research Scholar, [4]Director, CFSL/CBI/New Delhi

Corresponding Author: Komal Yadav

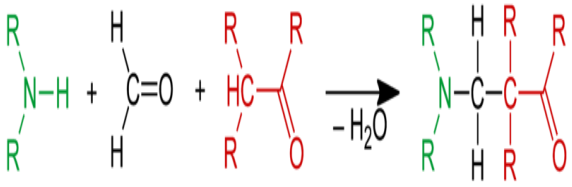
ABSTRACT

A Mannich base from the reaction of *p*-chlorobenzaldehyde, acetophenone and *p*-toluidine was obtained by using $EtAlCl_2$ as catalyst. The formation of this Mannich base is an organic reaction which consists of amino alkylation of an acidic proton placed next to a carbonyl group by formaldehyde and a primary or secondary amine, and then the final product formed is a β-amino-carbonyl compound known as Mannich base. Here we have taken *p*-chlorobenzaldehyde in place of formaldehyde and p-toluidine as an amine. This reaction is known as Mannich reaction. The compound formed from this reaction was then duly characterized on the basis of IR, ^{1}H-NMR studies; strong bonds of the compounds are shown in the spectras. And then, biological screening was carried out against E.coli and staphylococcus aureus and the compound was found to be active against E.Coli and staphylococcus aureus. The Mannich-Reaction is employed in the organic synthesis of natural compounds such as peptides, nucleotide, antibiotics, and alkaloids (e.g. tropinone). Other applications are in agro chemicals such as plant growth regulators, paint- and polymer chemistry. As the formed compound was biologically active so it can be used as a pharmaceutical product also. So we can say that the compound formed by using *p*-chlorobenzaldehyde, acetophenone, and *p*-tolouidine was found to be a biologically active compound on E.coli and staphylococcus aureus. And it was also concluded that $EtAlCl_2$ can also be used as a catalyst for synthesizing a Mannich base as it was proved in this reaction that by using $EtAlCl_2$ as a catalyst a compound i.e. a Mannich base can be synthesized successfully and its properties are also mentioned below and also its biological applications were also found.

Key Words: Mannich base, β-amino-carbonyl compound, p-toluidine, $EtAlCl_2$

INTRODUCTION

The Mannich reaction is an organic reaction which consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group by formaldehyde and a primary or secondary amine or ammonia. The final product is a β-amino-carbonyl compound also known as a Mannich base. Reactions between aldimines and α-methylene carbonyls are also considered Mannich reactions because these imines form between amines and aldehydes. The reaction is named after chemist Carl Mannich.

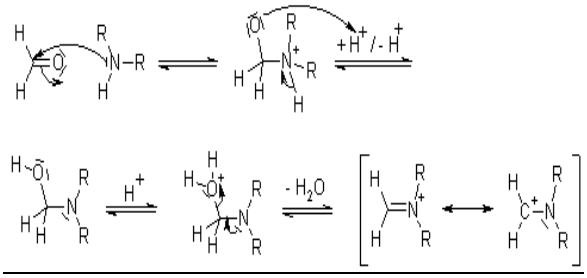


The Mannich reaction is an example of nucleophilic addition of an amine to a carbonyl group followed by dehydration to the Schiff base. The Schiff base is an electrophile which reacts in the second step in an electrophilic addition with a compound containing an acidic proton (which is, or had become an enol). The Mannich reaction is also considered a condensation reaction.

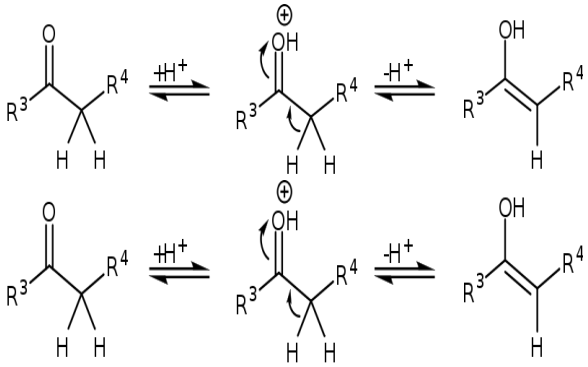
In this reaction, primary or secondary amines or ammonia, are employed for the activation of formaldehyde. Tertiary amines lack an N–H proton to form the intermediate enamine. α-CH-acidic compounds (nucleophiles)

include carbonyl compounds, nitriles, acetylenes, aliphatic nitro compounds, α-alkyl-pyridines or imines. It is also possible to use activated phenyl groups and electron-rich heterocycles such as furan, pyrrole, and thiophene. Indole is a particularly active substrate; the reaction provides gramine derivatives.

Mechanism of the Mannich Reaction:

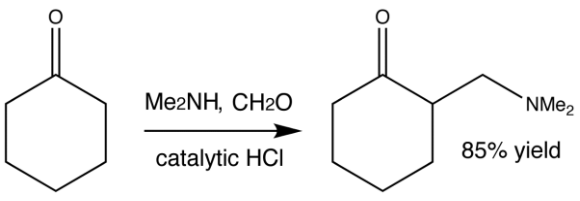


The compound with the carbonyl functional group (in this case a ketone) can tautomerize to the enol form, after which it can attack the iminium ion.

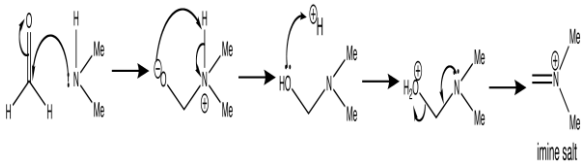


Example of a Mannich reaction:

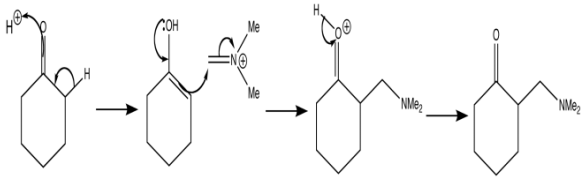
This is a typical example of a Mannich reaction. It involves an enolizable aldehyde or ketone, a secondary amine, formaldehyde as its aqueous solution, and catalytic HCl. The product is an amino-ketone from the addition of one molecule each of formaldehyde and the amine to the ketone.



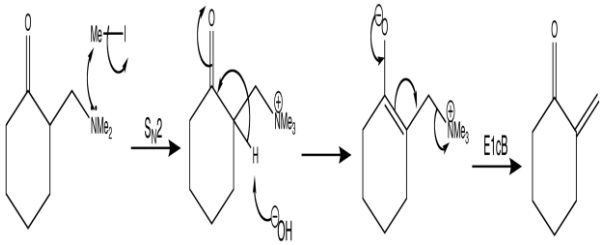
Step 1: Imine formation



Step 2: Addition of imine salt to ketone

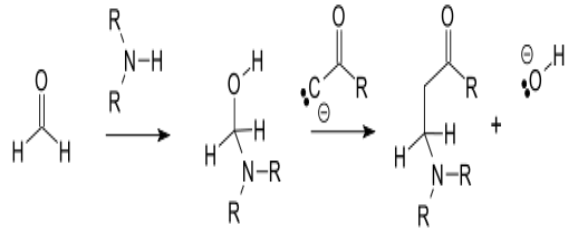


The Mannich products can be converted to enones. Enones such as that shown below, with two hydrogen atoms at the end of the double bond are called exo-methylene compounds. Whilst they are very reactive, they cannot easily be made or stored.



Mannich Base

Ketonic amines prepared from the condensation of a ketone with formaldehyde and ammonia or a primary or secondary amine. A Mannich base can act as the equivalent of an α, β unsaturated ketone in synthesis or can be reduced to form physiologically active amino alcohols.



Reactivity:

With primary or secondary amines, Mannich bases react with additional aldehyde and carbon acid to larger adducts $HN(CH_2CH_2COR)_2$ & $HN(CH_2CH_2COR)_2$. With multiple acidic hydrogen atoms on the carbon acid higher adducts are also possible.

Ammonia can be split off in an elimination reaction to form enals and enones.

Applications Of Mannich Reaction

The Mannich reaction is employed in the organic synthesis of natural compounds such as peptides, nucleotides, antibiotics and alkaloids. The Mannich reaction is also used in the synthesis of medicinal compounds e.g. fluoxetine (antidepressant), tramadol and tolmetin (anti-inflammatory).

METHODOLOGY

SYNTHESIS OF MANNICH BASE:-

p-cholorobenzaldehyde (0.397gm) dissolved in CH_2Cl_2 (5mL) stirred for ½ hr, followed by addition of $EtAlCl_2$ (0.76mL). The resulting solution was stirred for another ½ hr. A solution of *p*-toluidine (0.303gm) in CH_2Cl (5mL) was added to the above mixture and again stirred for ½ hr. Now acetophenone (0.33 mL) in CH_2Cl_2 (5mL) was added and reaction mixture was refluxed over water bath for 2-3 hrs. Completion of reaction was checked by TLC. The reaction mixture was now kept overnight. Reaction mixture was quenched with saturated solution of NH_4Cl and compound was extracted with CH_2Cl_2 , the organic phase was washed with water and finally dried over sodium sulphate and concentreated to ~ 2 mL and left at room temperature for crystallization.

Fine crystals deposited were found which were separated, washed with few drops of cold CH_2Cl_2 and finally dried.

CHROMATOGRAPHIC STUDY OF SYNTHESIZED MANNICH BASE:-

Formation of synthesized Mannich base was checked by running TLC in 5% ethyl acetate and 95% petroleum ether and viewed in Iodine chamber.

BIOLOGICAL ACTIVITY OF MANNICH BASE:-

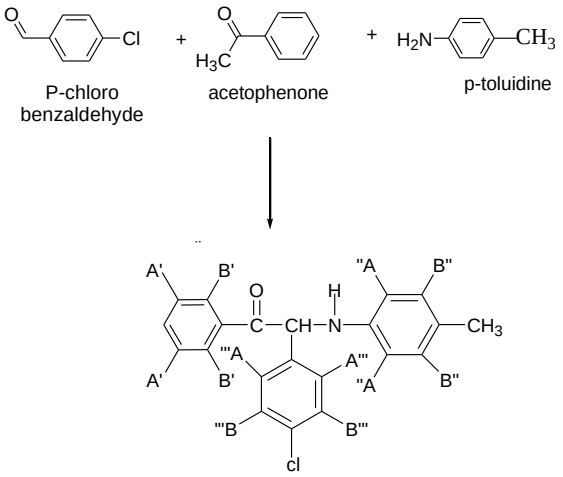
Nutrient agar dissolved in distilled water was autoclaved at 121^0c for 30 mins at 15 Psi. Now the media was poured in petriplate in LAF. Vials were created and the bacteria were spreaded with sterile glass spreader. Compound, solvent and antibiotic (each 100µL) was incorporated into vials. Incubated the plates at 37^0c for 24 hrs, measured the zone and calculated the % activity.

SPECTRAL STUDIES:-

- **IR Spectra-**
  Infra red spectra of compound have been recorded using KBr discs in the range of 2000-450 cm^{-1} with Shimadzu 8300FT-IR spectrophotometer.
- **^{1}H-NMR Spectra-**
  ^{1}H-NMR spectra were recorded on Bruker-DPX-300 at observation frequency 300-400 Hz using TMS as internal reference.

RESULT

➢ **Synthesis of Mannich base:**

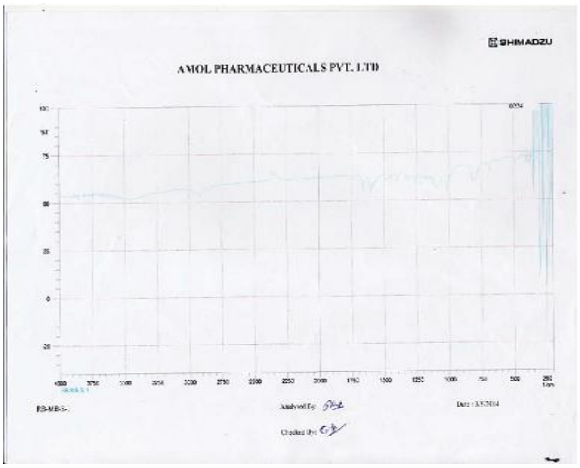


➢ **Physiochemical studies of the synthesized Mannich base:**

S.No	Characterstics	Resuts
1.	Physical state	Solid
2.	Colour	Light yellow
3.	Yield	0.457g
4.	% Yield	32%
5.	Melting point	65^o -70^o c

➢ **SPECTRAL INTERPRETATION OF SYNTHESIZED MANNICH BASE:-**

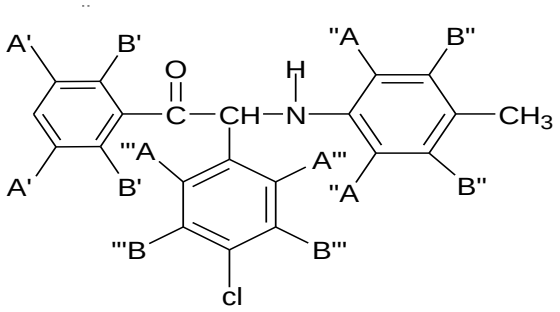
IR Spectra-

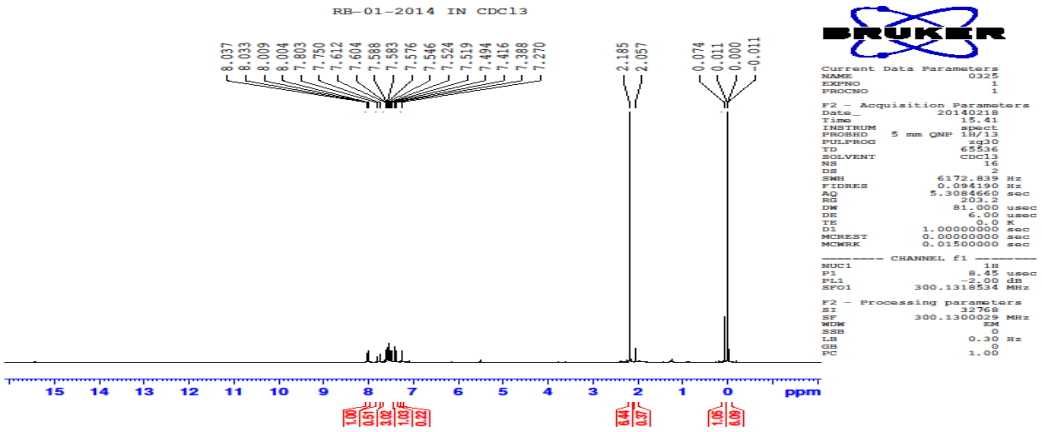


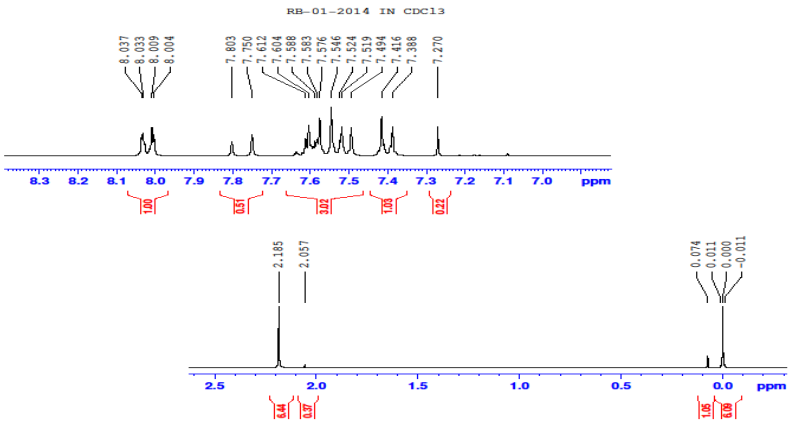
Strong absorption band at 1695 cm^{-1} confirms the presence of carbonyl group. The absorption band between 1600-1500 cm^{-1} results due to aromatic skeletal vibration.

^{1}HNMR Spectra-

Two doublet are obtained at δ 8.02 and δ 7.59,(d, $^{3}J_{HH}$ = 8.02 Hz, 2H), of proton A´A´ and B´B´ of phenyl ring, similarly the protons of cl-ph ring gives doublet at δ 8.01 and δ 7.50 (d, $^{3}J_{HH}$ = 8.7Hz) due to A´´´A´´´ and B´´´ B´´´. The protons of *p*-toluidine moiety gives doublet at δ 7.57 and 7.40 (d, $^{3}J_{HH}$ =8.4Hz) due to A´´A´´ and B´´B´´.







BIOLOGICAL ACTIVITY

- % Activity of compound with antibiotic against *E.Coli*.

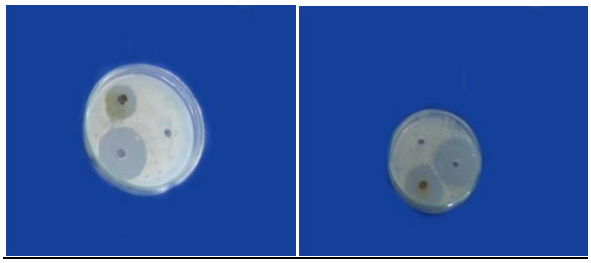


Table 1: Measured zone detail against *E.coli.*

Name of bacteria	Plate I (Zone in mm)			Plate II (Zone in mm)		
	Antibiotic (Amoxicillin)	compound	Solvent ($CDCl_2$)	Antibiotic (Amoxicillin)	Compound	Solvent ($CDCl_3$)
E.coli	42	24	0	42	28	0

Plate I % activity = 57.14%
Plate II % activity =66.6%
Mean = 61.8%

- % Activity of compound with antibiotic against *Staphylococcus aureus* –

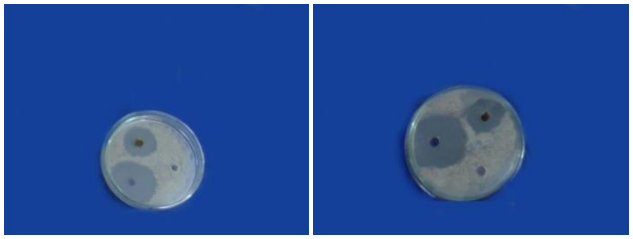


Table 2: Measured zone details against *Staphylococcus aureus*

Name of bacteria	Plate I (Zone in mm)			Plate II (Zone in mm)		
	Antibiotic (Amoxicillin)	compound	Solvent ($CDCl_2$)	Antibiotic (Amoxicillin)	Compound	Solvent ($CDCl_3$)
Staphylococcus aureus	42	24	0	42	24	0

Plate I % activity = 57.14%
Plate II % Activity = 57.14%
Mean=57.1

DISCUSSION

A Mannich base can be synthesized in laboratory by using $EtAlCl_2$ as a catalyst and *p*-toluidine, *p*- chlorobenzaldehyde and acetophenone as reagents. The structure was duly characterized by ^{1}H-NMR and IR spectras and the synthesized Mannich base can be used as a pharmaceutical product as it was found to be active on *E.coli* and *staphylococcus aureus.*

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